Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The amendment to the specification is made to correct three typographical errors appearing in the amended paragraph. The amendments to SEQ ID NO: 8 and SEQ ID NO: 12 find descriptive support in SEQ ID NO: 1 as filed. The remaining amendment harmonizes the span of the residues appearing in SEQ ID NO: 17 to the corresponding sequence within SEQ ID NO: 1. Therefore, no new matter has been entered. Accompanying this amendment is a corrected Sequence Listing, along with a diskette containing the computer readable form, and a Statement Under 37 CFR § 1.821.

The rejection of claims 1, 2, and 8-12 under 35 U.S.C. § 112 (first paragraph) for lack of enablement is respectfully traversed in view of the above amendments and the following remarks.

With respect to the issue concerning which biliverdin reductase ("BVR")-encoding nucleotide sequence was utilized by the applicant in the examples to the present application, applicant notes that the description of the figures (which correspond to the example) describes the transfected HeLa cells as having been transfected with human BVR DNA (*see* page 3, lines 24-25). The specification discloses SEQ ID NO: 2 as an exemplary nucleic acid encoding human BVR. The accompanying Declaration of Mahin D. Maines Under 37 C.F.R. § 1.132 ("Maines Decl.") at paragraph 5 confirms that in performing the experimental work reported in the example, Dr. Maines used the human BVR DNA sequence that is reported in the application as SEQ ID NO: 2. No other human BVR DNA sequence is explicitly recited in the present application (*Id.*).

Applicant submits that the results achieved with the human BVR of SEQ ID NO: 2 are sufficiently predictive of results that would be expected when practicing the invention with other mammalian BVR. In support of this position, the enclosed Maines Declaration demonstrates that the structure and function of BVR proteins are highly conserved among mammalian BVR and, therefore, results achieved with human BVR are predictive of results that can be achieved with other mammalian BVR (Maines Decl. ¶ 4).

The present application identifies two human BVR amino acid sequences (SEQ ID NO: 1 and SEQ ID NO: 3) and a single rat BVR amino acid sequence (SEQ ID NO: 4) (Maines Decl. ¶ 6). The two human BVR sequences are 99 percent identical (*Id.*). The human BVR of SEQ ID NO: 1 and the rat BVR of SEQ ID NO: 4 are 82 percent identical

(*Id.*). Mammalian BVR proteins are characterized by a number of shared structural features (*see* Maines Decl. ¶ 7). In comparing the human BVR sequence of SEQ ID NO: 1 and the rat BVR sequence of SEQ ID NO: 4, the rat sequence contains an identical hydrophobic domain, an identical nucleotide binding domain, an identical oxidoreductase domain, a conserved leucine zipper domain (i.e., with any residue variations being between L and K residues), identical or conserved kinase motifs, an identical nuclear localization signal, an identical myristylation site, a conserved zinc finger domain, a conserved PKC enhancing domain, and a conserved PKC inhibiting domain (*Id.*). Based on the shared or conserved structural features between the human and rat BVR sequences, one of ordinary skill in the art would expect other mammalian BVR sequences to share these same identical or conserved structural features (*Id.*).

The reasonableness of the expectation of shared structural features, based on a comparison of human and rat BVR sequence, is confirmed by the alignment of human and rat BVR sequences with the mouse and pig BVR sequences, which have subsequently been obtained in Dr. Maines' laboratory (*see* Maines Decl. ¶ 8). The mouse and pig BVR amino acid sequences were aligned with the human and rat BVR amino acid sequences using the ClustalW alignment program set on its default settings (*Id.* and Exhibit 3 thereto). The mouse BVR sequence is about 81 percent identical to the human BVR sequence of SEQ ID NO: 1 (Maines Decl. ¶ 9). Based on the alignment shown as Exhibit 3 to the Maines Declaration, one of ordinary skill in the art would conclude that mouse BVR, when compared to the human BVR of SEQ ID NO: 1, contains an identical hydrophobic domain, an identical nucleotide binding domain, an identical oxidoreductase domain, a conserved leucine zipper domain (i.e., with any residue variations being between L and K residues), identical or conserved kinase motifs, a conserved nuclear localization signal, an identical myristylation site, a conserved zinc finger domain, an identical PKC enhancing domain, and a conserved PKC inhibiting domain (*Id.*). This high structural conservation, particularly within previously identified functional domains of the protein, indicates that the proteins are functionally quite similar (*Id.*). The pig BVR sequence is about 98 percent identical to the human BVR sequence of SEQ ID NO: 1 (Maines Decl. ¶ 10). Based on the alignment shown as Exhibit 3 to the Maines Declaration, one of ordinary skill in the art would conclude that the pig BVR, when compared to the human BVR of SEQ ID NO: 1, contains an identical hydrophobic domain, an identical nucleotide binding domain, an identical oxidoreductase domain, a conserved leucine zipper domain (i.e., with any residue variations being between L and K residues), identical or conserved kinase motifs, an identical nuclear localization signal, an identical myristylation site, a conserved zinc finger domain, an identical PKC enhancing

domain, and an identical PKC inhibiting domain (*Id.*). This high structural conservation, particularly within previously identified functional domains of the protein, indicates that the proteins are functionally quite similar (*Id.*).

In addition, based on the known biochemical pathways shared by mammalian BVR proteins, one of ordinary skill in the art would have expected the results achieved with one mammalian BVR to be consistent with other mammalian BVR (Maines Decl. ¶ 11). Prior to Dr. Maines co-pending application (U.S. Patent Application Serial No. 09/606,129, filed June 28, 2000), it was widely believed that BVR was a general housekeeping enzyme that was conserved among mammals, catalyzing the NADPH-dependent reduction of biliverdin to produce bilirubin (*Id.*). In particular, Noguchi et al., "Purification and Properties of Biliverdin Reductase from Pig Spleen and Rat Liver," *J. Biochem.* 86(4):833-848 (1979)("Noguchi")(copy attached as Exhibit 6 to the Maines Declaration) reports that purified pig and rat BVR has both NADH- and NADPH-dependent activities in converting biliverdin to bilirubin, with the NADH-dependent activity being optimal at pH 6.9 and the NADPH-dependent activity being optimal at pH 8.5 (*Id.*). Noguchi also indicates that both systems are inhibited by bilirubin, but inhibition of the NADPH-dependent activity was more pronounced (*Id.*). In addition, Noguchi reports that the NADPH-dependent activity for biliverdin had a K_m of 0.3 μM whereas the NADH-dependent activity for biliverdin had a K_m of 1-2 μM (*Id.*). Rigney et al., "The Reaction Mechanism of Bovine Kidney Biliverdin Reductase," *Biochim. Biophys. ACTA* 957:237-242 (1988)(copy attached as Exhibit 7 to Maines Declaration) reports that purified bovine BVR has both NADH- and NADPH-dependent activities in converting biliverdin to bilirubin, with the NADH-dependent activity being optimal at pH between 6 and 7 (depending on the buffer system utilized) and the NADPH-dependent activity being optimal at pH 8.5 (*Id.*). Rigney et al., "The Kinetics of Ox Kidney Biliverdin Reductase in Pre-steady State: Evidence That the Dissociation of Bilirubin is the Rate-determining Step," *Biochem J.* 259:709-713 (1989)(copy attached as Exhibit 8 to Maines Declaration) confirms that the broad features of the reaction mechanism for NADPH- and NADH-dependent activities are the same, with BVR activity exhibiting a pH-dependent burst in the rate of conversion of biliverdin to bilirubin followed by a steady-state rate (*Id.*). As addressed in the present application, at Example 1, human BVR shares the property of dual co-factor activity using NADPH and NADH (*Id.*). In addition to the conserved activity among mammalian BVR, Rigney et al., "Some Physical and Immunological Properties of Ox Kidney Biliverdin Reductase," *Biochem J.* 255:431-435 (1988)(copy attached as Exhibit 9 to Maines Declaration) reports that antibodies raised against ox BVR were able to

immunoprecipitate BVR from numerous mammals, including pig, guinea pig, mouse, rat, hamster, fox, wallaby, and human (*Id.*). All of the foregoing confirms that those persons of skill in the art believed BVR to be functionally well-conserved among mammals (*Id.*).

Thus, based upon the high degree of structural similarity of the three BVR proteins identified in the present application, as confirmed by their high degree of structural similarity with mouse and pig BVR sequences, and the functional similarity of many mammalian BVR proteins, persons of skill in the art would have expected results achieved with any one mammalian BVR protein to be achievable with other mammalian BVR proteins (Maines Decl. ¶ 12).

In view of all of the foregoing, applicant submits that the rejection of claims 1, 2, and 8-12 under 35 U.S.C. § 112 as lacking enablement is improper and should be withdrawn.

The rejection of claims 1, 2, and 8-12 under 35 U.S.C. § 112 (first paragraph) as lacking written descriptive support is respectfully traversed.

Applicant submits that the demonstration in the present application of conservation among rat and human BVR would have allowed one of ordinary skill in the art to conclude that applicant was in possession of the presently claimed invention, because the present application sets forth three species within the scope of the recited genus of 'mammalian BVR', and identifies structural features characteristic of 'mammalian BVR'. That the present application supports the claim language 'mammalian BVR' is entirely consistent with the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099 (January 5, 2001) ("Written Description Guidelines"), because the present application describes "a representative number of species."

The burden of establishing that an application lacks adequate written descriptive support falls on the PTO. *See In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("[T]he PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims."). In this case, the only assertion made by the PTO to support its conclusion is the absence of data recited in the examples that confirm other mammalian BVR possess the claimed activity. Thus, the PTO cites no directly relevant evidence that the three disclosed species are not representative of the recited genus. However, the present application presents *direct* evidence of the structural and functional features shared by the three exemplary members of the recited genus (which, applicant submits, would allow one of

ordinary skill in the art reasonably to conclude that applicant was in possession of the recited genus). Despite the overwhelming evidence that the three disclosed species appear to share identical hydrophobic domains, identical nucleotide binding domains, identical oxidoreductase domains, conserved leucine zipper domains, conserved kinase motifs, identical nuclear localization signals, identical myristylation sites, conserved zinc finger domains, conserved PKC enhancing domains, and conserved PKC inhibiting domains (*see* page 16, lines 8-33), the PTO concludes that this is insufficient.

Nowhere has the PTO presented evidence that the three species of mammalian BVR are *not* representative of the recited genus, as required by *In re Wertheim*. Instead, the PTO has apparently taken the position that three species is simply inadequate given the size of the recited genus. The Written Description Guidelines indicate that when the genus represents widely variant species more than one species is required, yet when the genus represents closely related species as few as one species may be sufficient. 66 Fed. Reg. at 1106. Thus, size of the genus is clearly of less import than variance of species within the genus. In this case, the *direct* evidence presented in the specification demonstrates that structural and functional variance is at a minimum. The PTO, in sharp contrast to applicant, has provided no evidence concerning variance within the genus.

In addition to the foregoing and as further support for the fact that the three species *are* representative of the recited genus of mammalian BVR, the Maines Declaration—for the reasons noted above—supports the conclusion that the structure and function of BVR proteins is highly conserved among mammalian BVR and, therefore, results achieved with human BVR are predictive of results that can be achieved with other mammalian BVR.

For these reasons, the rejection of claims 1, 2, and 8-12 under 35 U.S.C. § 112 as lacking written descriptive support is improper and should be withdrawn.

In view of all of the foregoing, applicant earnestly submits that this case is in condition for allowance.

Respectfully submitted,

Dated: March 11, 2004

Edwin V. Merkel
Registration No. 40,087

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1128
Facsimile: (585) 263-1600

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Wendy L. Barry